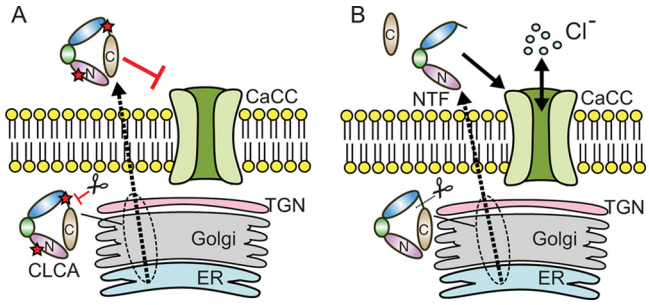
Papers of the Week

Unmasking How Chloride Channel Calcium-activated Proteins Mediate Mucus Production ♦

♦ See referenced article, *J. Biol. Chem.* 2012, **287,** 42138–42149

Self-cleavage of Human CLCA1 Protein by a Novel Internal Metalloprotease Domain Controls Calcium-activated Chloride Channel Activation

Chloride channel calcium-activated (CLCA) proteins are critical in controlling the production of mucus in respiratory and other organ systems. These secreted proteins regulate chloride transport and mucin expression. One of them, CLCA1, plays an important, but poorly understood, role in cystic fibrosis, asthma, and other lung diseases that overproduce mucus. In this Paper of the Week, a team led by Tom J. Brett at the Washington University School of Medicine in St. Louis demonstrated that CLCA proteins contain a consensus proteolytic cleavage site that is recognized by a novel zinc metalloprotease domain in the N terminus of the proteins themselves. CLCA1 mutations that interfere with the self-cleavage process prevent chloride transport through the channel. The cleavage normally exposes the N-terminal fragment of CLCA1, which can independently gate the channel. The authors conclude, "These data provide both a mechanistic basis for CLCA1 self-cleavage and a novel mechanism for regulation of chloride channel activity specific to the mucosal interface."



A, CLCA1 variants with inhibitory mutations in the metalloprotease domain or cleavage site (*red stars*) are secreted as full-length molecules, which are unable to productively interact with a chloride channel due to masking by the C-terminal portion of CLCA1. *B*, native CLCA1 undergoes self-cleavage in the secretory pathway, releasing the C-terminal fragment and allowing for the N-terminal fragment to engage and activate a chloride channel.

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